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Chapter 4

Radionuclide Pain Palliation Treatment and Radiosynovectomy

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Abstract

The main nuclear medicine palliation treatment methods are radionuclide pain palliation treatment in cases of disseminated painful bone metastases and radiosynovectomy in inflammatory arthritis cases. Both methods can be easily administered and do not require long-term hospitalization. They are reliable with high palliation value and low complication rates.

Keywords: radiosynovectomy, radionuclide pain palliation treatment, therapy response

1. Radionuclide pain palliation treatment

1.1. Introduction

Painful bone metastases are one of the most common causes of morbidity in metastatic cancer patients. The vast majority of these patients need multiple medical treatments. The most common tumors, which cause painful bone metastases, are breast, prostate, lung, and renal tumors [1]. If not diagnosed or sufficiently treated, painful bone metastases cause severe pain, spinal cord compression, hypercalcemia, and pathological fractures. In many studies, a direct correlation has been determined between bone metastasis load and survival [2]. The majority of bone metastases are localized in the axial skeleton due to the presence of bone marrow [3]. Generally, bone metastases are classified as osteoblastic, osteolytic, or mixed type. Although some tumors have pure blastic or lytic metastases, the metastases of many tumors are of mixed phenotype [4].

Pain associated with bone metastases is generally seen in two different forms. The nature of the first is related with bone remodeling, and chronic pain due to inflammatory reaction in and around the metastatic focus. The nature of the second type of pain is more severe and is acute pain exacerbated by physical activity or patient position [5, 6]. Non-steroid or narcotic analgesics and external beam radiotherapy (EBRT) are the most commonly used therapy methods for the palliation of metastatic bone pain [7]. Although conventional radiotherapy is an effective method in the palliation of symptoms from bone metastasis, many patients have painful bone metastases in many different regions of the skeletal system [8]. Although wide-field radiations such as hemibody radiotherapy are also effective, they are not preferred due to technical difficulties and radiation toxicity [9, 10]. Systemic therapy management should be preferred for patients with diffuse symptomatic bone involvement. In these patients, intravenous bisphosphonates may have a role in the reduction of the development of complications.

1.2. Treatment

In the last few decades, different radionuclides have been used for radionuclide pain palliation. Radionuclides are usually administered intravenously and are quickly localized in regions of active bone reaction and remodeling. Radionuclide pain palliation treatment is indicated in patients with multiple bone metastases shown on bone scintigraphy and in cases that cannot be treated with non-steroidal or narcotic analgesics or who are resistant to these treatments [11]. In the presence of epidural spinal cord pressure, active pathological fracture, renal failure, pregnancy, and lactation, treatment is not recommended. Patients with uncontrolled non-skeletal metastasis, asymptomatic bone metastases, ≤3 bone metastases, purely osteolytic lesions, and patients with a shorter life expectancy (<2 months) are relatively contraindicated. The physical properties of radionuclides used in radionuclide pain palliation are shown in **Table 1**.

Radionuclide	Half life (days)	Decay type	Mean energy (keV)	Mean penetration depth (mm)	Gamma ray
Phosphor-32 [P-32]	14.3	β-	695	3.0	Yok
Strontium-89 [Sr-89]	50.5	β-	580	2.4	Yok
Samarium-153 [Sm-153]	1.9	β-	233	0.5	Var
Renium-186 [Re-186]	3.7	β-	349	1.1	Var
Renium-188 [Re-188]	0.7	β-	2120	3.0	Var
Tin-177m [Sn-177m]	13.6	CE	127	<0.1	Yok
Radium-223 [Ra-223]	11.4	α	5850	<0.1	Var

β- = beta ray, CE = conversion electron, α = alpha ray.

Table 1. The physical properties of the radionuclides used in pain palliation treatment.

The radionuclides used in radionuclide pain palliation act through two main mechanisms. The first group is attracted to calcium and directly localizes to the bone matrix. The other group is applied as chelate with organic phosphates and is added to the bone matrix [11]. Gama-emitting radionuclides provide post-therapy imaging on gamma cameras.

1.3. Follow-up

No special radiation safety precaution is necessary because the emission rates of the radionuclides used for pain palliation are very low. Therefore, hospitalization is not required for treatment. The patient can be quickly mobilized after several hours of treatment. The administration takes approximately 1 min as an intravenous injection followed by a 20–30-ml saline wash through the vein. The patient is then advised to take oral hydration and make frequent toilet trips for a few hours. Following the treatment, a weekly complete blood count for an 8-week period is recommended. Transient myelosuppression can be monitored. Thrombocytopenia is the most common finding, which is characterized by a 40–60% decrease in platelet count compared to the baseline value. Most cases have grade 1 or 2 toxicity. Neutropenia and anemia are rare.

A decrease in the pain of the patient is expected at 1–3 weeks after treatment, although it varies according to the radionuclide used [12]. Positive response to therapy has been reported as 60–92%, although it can vary according to the primary malignancy and the spread of the disease [13–21]. Flare phenomena can be observed as an increase in pain which is severe but usually self-limiting during 24–48 h after treatment. Patients with flare phenomena have been shown to have a better response rate to treatment compared to those where it is not experienced. Palliation times of up to 6 months have been reported following radionuclide treatment. Different pain-scoring systems and patient questionnaires can be used to evaluate treatment response [22]. It is also helpful to evaluate the patient's narcotic analgesic needs. Pain scoring systems and quality of life questionnaires that can be used for this purpose are presented in **Table 2**.

Serafini et al. compared Sm-153 EDTMP with a placebo in bone metastases of solid tumor in a randomized, prospective study and showed that patients receiving higher doses of Sm-153 responded better at all times (1–4 weeks) than those who had received the placebo. In two-thirds of the patients evaluated, the response to treatment was in the fourth week and palliation continued until the 16th week [23].

Visual Analog Scale for Pain (VAS Pain)
Numeric Rating Scale for Pain (NRS Pain)
McGill Pain Questionnaire (MPQ)
Short-form McGill Pain Questionnaire (SF-MPQ)
Chronic Pain Grade Scale (CPGS)
Short Form-36 Bodily Pain Scale (SF-36 BPS)
Physician's Global Assessment of Pain (PGA)

Table 2. The scoring systems that can be used in the evaluation of pain palliation pretreatment and of the response to treatment.

Sartor et al. reported a significantly better objective response rate in a double-blind randomized study of patients with bone metastasis of prostate cancer where Sm-153 was compared with a placebo. The objective response rates of the Sm-153 group were reported to be better [24]. Several studies have reported that the use of Sm-153 in repeated doses and in combination with different chemotherapy regimes was more reliable [25–28]. During treatment with Sr-89 in prostate cancer cases, a single-dose relationship was shown and doses reaching 10.8 mCi were not determined to affect survival [29]. However, application combined with chemotherapy was determined to remove both the efficacy of pain palliation and survival [30–32]. In two randomized studies, Sr-89 and EBRT were applied alone and similar rates of pain palliation were obtained, but it was shown that after treatment with Sr-89, there was a lower possibility of the development of new painful bone metastasis [33, 34]. Radium-223 has started to be used in recent years, and according to the results of the first studies, it is a radionuclide that extends survival in addition to providing pain palliation. In prostate cancer cases, it has been shown to provide prolonged survival, and reduced levels of PSA and ALP compared to a placebo and no difference has been observed in hematological toxicity [35].

In summary, radionuclide pain palliation treatment is an effective method in patients with osteoblastic, widespread painful bone metastasis. The simple and systemic application provides the significant advantage of allowing treatment of all the painful lesions of the patient. It is a safe method with low rates of side effects even when applied at repeated doses or combined with different chemotherapy regimes.

2. Radiosynovectomy

2.1. Introduction

The use of radionuclides was first described in 1963 with the use of Au-198 in the treatment of persistent knee effusion in arthritis treatment. However, as Au-198 particles are very small, their leakage outside the knee joint caused severe clinical side effects [36]. In subsequent years, Yttrium-90 [Y-90], colloidal P-32, and Re-186 sulfide colloid were radionuclides which came to be often used for radiosynovectomy. In the last 20 years, Erbium-169 citrate [Er-169] has started to be used in small joints [37–39].

Due to proliferation and hyperperfusion in synovial tissue in inflammatory arthritis, there is effusion, macrophage accumulation, and the expression of inflammatory cytokines in the joint space. Consequently, pain, loss of movement, and in long term, arthrosis are observed in the affected joint. Radiosynovectomy is effective in approximately 80% of rheumatoid arthritis patients. In developed countries, there is increasing use of radiosynovectomy because of pain and restricted movement in osteoarthritic joints which occur with increasing life expectancies. The current most common indications for application are rheumatoid arthritis, psoriatic arthritis, osteoarthritis, hemophilic arthritis, and villonodular synovitis. The radionuclides widely used for radiosynovectomy and their physical properties are shown in **Table 3**. Due to the energy and soft-tissue penetration properties, Er-169 is used in small joints, Re-186 and P-32 in medium-sized joints, and Y-90 in large joints [40, 41].

Radionuclide	Half life (days)	Soft-tissue penetration (mm)	Energy (MeV)
Er-169	9.5	0.3–1	0.34
Re-186	13.7	1.2–3.7	0.98
Au-198	2.7	1.2–3.6	0.96β–0.41γ

Table 3. The physical properties of the radionuclides used for radiosynovectomy.

2.2. Treatment

In radiosynovectomy, particles of 0.05–2 μm in size are applied directly into the joint space. After application, the particles reaching the synovia are phagocytized by macrophages and other inflammatory cells. The absorption by the synovia of a dose of approximately 100-Gy radiation results in synovectomy similar to surgical synovectomy. As beta particles have tissue penetration up to a maximum of 10 mm, the surrounding soft tissues are protected from radiation damage [42]. Pregnancy, breastfeeding, local infection, massive hemarthrosis, or ruptured Baker cyst are contraindications for radiosynovectomy.

2.3. Follow-up

After treatment, it is recommended that the joint is immobilized for 48 h. If a sufficient response is not observed after the first application, radiosynovectomy can be reapplied three times at a 3-month interval. Repeated doses are more effective than a single, high-dose application. Side effects following radiosynovectomy have been reported to be extremely rarely. These may include infection, thrombosis, and skin necrosis caused by extra-articular application [43]. To prevent thrombosis, the use of heparin is recommended in the immobilization period. The response to treatment is closely related to the degree of synovitis, the level of arthrosis pretreatment, and in rheumatoid arthritis cases, the level of systemic inflammation. The highest response rates have been reported in cases of hemophilic arthritis [44, 45]. If treatment is applied in the early stages of arthrosis, the success rates are high, with response rates of 73% reported in cases of early stage rheumatoid arthritis [46]. In cases of radiosynovectomy applied to the knee joint because of osteoarthritis, the response rate has been reported as 40–85% [46].

These serious differences in rates in the evaluation of treatment response are due to the fact that objective scoring systems have not been used. In the evaluation of the response to treatment following radiosynovectomy, physical examination, clinical scoring systems, and radiological response criteria can be used. In the physical examination, swelling in the joint, pain, restricted movement, and weakness are evaluated as the response to treatment. In the clinical scoring system, treatment response is classified as excellent, good, fair, and ineffective. In a report of this scoring system applied to 577 patients, excellent and good responses were obtained in the knee joint in 57%, in the shoulder joint in 63%, the elbow in 61%, the wrist in 64%, finger joints in 54%, and metacarpophalangeal joints in 54% [47].

Another parameter used in the evaluation of response following radiosynovectomy is the Visual Analog Scale for Pain (VAS Pain). The VAS score of rheumatoid arthritis patients

at 6 months after radiosynovectomy has been determined to be improved by three stages compared to the pretreatment score [48]. As a more objective evaluation of response following radiosynovectomy, blood pool phase activity involvement on three-phase Tc-99m MDP bone scintigraphy can be used. Response has been determined in small joints at 81% and in large joints at 69% with Tc-99m MDP bone scintigraphy following radiosynovectomy [49]. Unlike cases of pigmented villonodular synovitis, the application of radiosynovectomy after surgical synovectomy has been shown to be more effective in resistant cases [50].

In conclusion, when the radionuclide is selected appropriate to the size of the joint, radiosynovectomy is a safe option in the treatment of inflammatory arthritis with high success and low complication rates.

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